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Selective Antimicrobial Modulation of the Intestinal Flora of Patients with Acute Nonlymphocytic Leukemia: A Double-Blind, Placebo-Controlled Study

H. F. L. Guiot, P. J. van den Broek, J. W. M. van der Meer, and R. van Furth

From the Isolation Ward, J. A. Cohen Institute of Radiopathology and Radiation Protection; and the Department of Infectious Diseases, University Hospital, Leiden, the Netherlands

Thirty-three patients with acute nonlymphocytic leukemia were studied during remission-induction treatment in a double-blind, placebo-controlled, randomized study to ascertain the effect on the incidence of infection of an oral regimen of selective antimicrobial modulation (SAM). A decrease in the number of major acquired infections was observed: three infections occurred in 16 patients receiving the SAM regimen compared with eight infections in 17 patients given the placebo. The reduction of infection was correlated with a reduction of fever, with a reduction of the frequency of administration of antimicrobial agents for the treatment of infection, and with the selective elimination of aerobic and facultative anaerobic gram-negative rods from the digestive tract. Substantial unfavorable side effects were not observed.

Patients with acute leukemia experience prolonged periods of neutropenia due to their disease or its treatment. For this reason they often develop serious infectious complications. Although antibiotic therapy has improved in recent years and the fatality rate has been decreased, infection is still an important cause of morbidity and mortality in patients treated for acute leukemia [1]. Prevention of infections by protective isolation and supression of intestinal flora probably reduces a part of the infectious problems.

Since 1976, infection prevention in the isolation ward of our hospital has consisted of protective isolation (laminar airflow rooms and food with a low bacterial level) and selective elimination of potentially pathogenic aerobic and facultative anaerobic bacteria from the skin and mucosal surfaces [2]. The combination of antimicrobial agents chosen for administration to the patients at risk has only limited or no activity against anaerobic bacteria [3]. The objective goal of this regimen of selective antimicrobial modulation (SAM) [3] (referred to as partial antibiotic decontamination elsewhere [2]) is to preserve colonization resistance [3, 4]. Colonization resistance refers to the resistance that microorganisms must overcome before they can colonize body surfaces [5]. The SAM approach seemed justified because aerobic bacteria are frequently involved in infectious complications in neutropenic patients, whereas the anaerobic bacteria seem to be relatively harmless [6].

From a previous study it was concluded that the SAM regimen prevents major infections in patients with severe bone-marrow failure [3], but it remained uncertain whether the SAM regimen would have the same favorable effect in hospitals with restricted facilities for protective isolation and bacteriologic control. The present study was performed to determine whether selective elimination of aerobic and facultative anaerobic gram-negative bacteria from the intestinal tract would reduce the number of infectious complications without the use of other sophisticated preventive measures.

In contrast to the previous study [3], no local antimicrobial treatment was applied to the oral cavity and skin, the patients were not isolated in laminar airflow rooms but were nursed in single-bed rooms, and patients were given conventional hospital food with some restriction of heavily contaminated food. Moreover, the attending physicians were not told the results of surveillance cultures of the patients.

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Please address requests for reprints to Dr. R. van Furth, Department of Infectious Diseases, University Hospital, Rijnsburgerweg 10, 2333 AA Leiden, the Netherlands.

The present report describes the results of this double-blind, placebo-controlled study on the efficacy of the SAM regimen in patients with acute nonlymphocytic leukemia who were nursed in conventional single-bed rooms.

Patients and Methods

Patient selection and randomization. All adult patients admitted between September 1977 and October 1981 with acute nonlymphocytic leukemia, and for whom a single-bed room was available, were eligible for the study. After informed consent was obtained, the patients were randomly assigned to receive the SAM regimen or placebo. Infection, fever, or other clinical complications present at the time of randomization did not exclude the patients from the study.

After randomization the patients were subjected to conventional physical and base-line bacteriologic examination. Simultaneously, or within a few days after the initial administration of the SAM regimen or placebo, therapy for leukemia was begun. Only patients who had received the SAM regimen for at least one week and patients with granulocytopenia (granulocyte count, <500/mm³) for at least one week were evaluated.

Infection prevention. Patients receiving SAM or placebo were nursed in conventional single-bed rooms. Persons entering a patient's room were required to wash their hands with povidone-iodine soap and to wear a mask and a gown that was only used in that room and that was replaced with a clean one at least once a day. The patients were not permitted to leave the room, except for examination elsewhere in the hospital or for a few days' stay at home (at most, for seven days) between two courses of cytostatic therapy. During the latter period the SAM regimen or placebo was continued at home. Both patient groups were given conventional hospital food with some restrictions concerning food assumed to be heavily contaminated (for example, raw meat and fish and deep-fried food from snack bars).

The SAM regimen consisted of four capsules (size, 6 × 18 mm) containing a mixture of neomycin, polymyxin B, and amphotericin B, given four times daily, and two capsules (size, 8 × 24 mm) containing nalidixic acid, given twice daily. The total dosage of these prophylactic antimicrobial drugs administered daily was 1 g of neomycin, 1 g of amphotericin B, 2 g of nalidixic acid (in the previous study [3], 4 g was given), and 400 mg of polymyxin B. The placebo consisted of capsules containing starch that were matched for size and color. All patients were treated locally in the nose with a cream containing 0.5% neomycin and 0.1% chlorhexidine hydrochloride to prevent carriage of *Staphylococcus aureus*. No other topical antiseptics were used.

The patients started their prophylactic regimen as soon as the base-line bacteriologic cultures had been obtained. If the clinical condition deteriorated because of the disease or antileukemic treatment, the patients were stimulated to swallow all of the capsules. When this was not possible, they were allowed to use fewer capsules during periods of chemotherapy. The capsules were swallowed whole, or they were opened and the contents were suspended in tea or another drink, which the patients drank during or after meals.

Prophylaxis or placebo was terminated and no further cytostatic therapy was given as soon as granulocyte counts exceeded 500/mm³ or if the attending physicians judged continuation of prophylaxis or placebo to be useless for clinical or psychological reasons.

Bacteriologic investigations. Bacteriologic surveillance cultures were obtained once a week and included cultures of urine, feces, and swabs taken from the nasopharyngeal, oropharyngeal, genitourinary, and perineal regions. The semiquantitative and qualitative bacteriologic techniques have been previously described [2]. The results of these surveillance cultures were not provided to the attending clinical staff. Bacteriologic examination for diagnostic purposes was performed when the clinical condition suggested bacterial infection.

Management of infection. In all patients, systemic antibiotic treatment was not instituted until infection was seriously suspected or proven. The choice of antibiotics was governed by the site of the infection and the suspected causative microorganisms. If the causative infectious agents were unknown, therapy almost always consisted of combinations of two antibiotics given iv. Whenever possible, antibiotic therapy was adjusted on the basis of the results of bacteriologic investigation.

Definition of infections. Infections were divided into bacterial, fungal, viral, and protozoan infections. The bacterial and fungal infections,

whether microbiologically proven or not, were divided into minor infections (clinically manifested infections of the skin or mucosa without extension to deep tissue, such as stomatitis, gingivitis, or pharyngitis) and major infections (infections with extension to the blood, deep tissues, or organs, such as pneumonia or pyelonephritis). Infections were called doubtful if the diagnostic procedures did not give conclusive results and the patient's clinical condition (fever) was the only suggestion of infection and if no response to antimicrobial therapy was observed.

Acquired infections were defined as infections showing their first clinical signs after the first week of the SAM regimen or placebo.

Fever. Each day on which a patient's axillary body temperature at least once was ≥38 C was defined as a day with fever. An axillary body temperature of >39 C was considered to be high fever.

Granulocytopenic episodes. A period of two or more successive days with granulocyte counts of <500/mm³ was defined as a granulocytopenic period.

Therapy for hematologic disease. All patients were treated with one or two remission-induction regimens. The LAM V treatment protocol (no. 06781) of the European Organization for Research on Treatment of Cancer (Zurich) consists of 1 mg of vincristine/m² of body surface area on day 1, 50 mg of doxorubicin/m² on day 2, and 80 mg of cytarabine/m² twice daily on days 3–9. The COAP protocol, which is less cardiotoxic, consists of 1.4 mg of vincristine/m² on day 1, 100 mg each of cyclophosphamide and cytarabine/m² on days 1–5, and 40 mg of prednisone/m² on days 1–5. In the present study, all patients received the LAM V treatment protocol except two, one in each group, who received the COAP protocol because of their advanced age.

Questionnaires. The patients were given a multiple-choice questionnaire after receiving the SAM regimen or placebo for three or more weeks. The questions concerned appetite and nausea.

Statistical evaluation. Statistical evaluation of differences was determined by Wilcoxon's two-sample test.

Results

Comparability of the randomized groups. Forty-two patients were randomized; 21 patients were allocated to receive the prophylactic regimen (SAM), and the other 21 patients received placebo. Five patients in the SAM group were excluded from the study because the period during which they received the SAM regimen or the period during which they were at risk was too short for evaluation (one week or less). In these patients prophylaxis was terminated on psychological grounds in one patient, because of a clinical condition too poor to permit cooperation in two patients, and because the granulocytopenic period was too short (fewer than seven days with granulocyte counts of <500/mm³) in the other two patients. In the control group four patients were excluded: one because of psychological reasons, one because the code was broken as the result of hearing loss (which was suspected to be due to neomycin), one because his poor clinical condition made it impossible for him to swallow the placebo for at least one week, and one because the granulocytopenic period lasted for fewer than seven days. The remaining patients, 16 in the SAM group and 17 in the placebo group, were comparable as to age, diagnosis, antileukemic therapy (table 1), and clinical condition at the time of randomization (table 2). No significant differences in the response to hematologic treatment and the number of granulocytopenic days, platelet transfusions, and days

Table 1. Clinical characteristics of patients with acute nonlymphocytic leukemia who received a regimen of selective antimicrobial modulation (SAM) or placebo.

Clinical characteristic	SAM group (16)	Placebo group (17)
Mean age in years (range)	49.4 (23–71)	48.5 (18–69)
Male:female ratio	7:9	7:10
Mean no. of days SAM regimen or placebo was given	50.4	45.5
Diagnosis		
Acute myelogenous leukemia	11	10
Acute myelomonocytic leukemia	4	7
Acute undifferentiated leukemia	1	0
Therapy		
LAM V protocol*	15	16
COAP protocol*	1	1
First remission induction	13	14
Second remission induction	2	3
Third remission induction	1	0

NOTE. Data are nos. of patients unless otherwise indicated.
* Described in Materials and Methods.

Table 2. Response to antileukemic therapy, hematologic data, and clinical course in patients with acute nonlymphocytic leukemia who received a regimen of selective antimicrobial modulation (SAM) or placebo.

Factor	SAM group (16)	Placebo group (17)
Response to therapy (no. of patients)		
Complete remission	8	8
Partial remission	3	3
No remission		
Discharged, clinical condition good	3	3
Discharged, clinical condition poor	2	2
Died of bleeding and infection	0	1
Mean no. (range) of patient-days with granulocyte counts of		
$<500/mm^3$*	35.1 (7–126)	28.5 (13–51)
$<100/mm^3$*	14.2 (0–31)	13.2 (0–24)
Platelet transfusions during days of SAM regimen or placebo (no. of transfusions per 100 days)	18.6	22.9

* Differences between the SAM and placebo groups are not statistically significant ($P > 0.60$ by Wilcoxon's two-sample test).

of the SAM regimen or placebo were observed between the two groups (table 2).

Efficacy of antimicrobial prophylaxis. Infection. It was assumed that the SAM regimen takes at least one week to become effective for the prevention of infection. Therefore, the first week of prophylaxis has been evaluated separately from the remaining period of the SAM regimen. In the first week, five of 16 SAM patients became infected or were already infected, and two SAM patients had fevers with unknown origins (table 3). One of these infections was a rectal abscess that, after drainage, was found to be caused by *Escherichia coli* and *Enterobacter cloacae*. The other infections were minor local infections in the oropharyngeal region. Seven of the 17 patients who received placebo became infected or were infected in the first week. One of these patients had septicemia due to *E. coli*, one had a rectal infiltrate, and one patient had a diverticulitis. The others had minor local infections in the oropharyngeal region (gingivitis, stomatitis, and pharyngitis). The differences concerning infectious complications between the two groups of patients during the first week are not significant ($P = 0.95$).

Table 3. Clinical condition of patients with acute nonlymphocytic leukemia during the first week of selective antimicrobial modulation (SAM) or placebo.

Clinical condition	SAM group (16)	Placebo group (17)
Minor infections		
Nasopharyngeal or oropharyngeal infection	4	3
Diverticulitis	0	1
Urinary tract infection	0	1
Major infections		
Septicemia	0	1
Rectal infection	1	1
Fever of unknown origin	2	0

NOTE. Data are nos. of patients.

Table 4. Infections acquired by patients with acute nonlymphocytic leukemia after the first week of selective antimicrobial modulation (SAM) or placebo.

Factor	SAM group (16)	Placebo group (17)
No. of patients with major infections due to gram-negative organisms	1*	7*
Total no. of clinically or bacteriologically documented infections	5	11
No. of major infections	3†	8†
Septicemia due to gram-negative bacteria‡	1	7
Septicemia due to *Streptococcus pneumoniae*	1	0
Pneumonia due to *Legionella pneumophila*	0	1
Rectal infiltrate	1	0
No. of minor infections	2	3
Nasopharyngeal or oropharyngeal infection	2	2
Urinary tract infection	0	1
Doubtful infections	3	3

* $P = 0.05$ by Wilcoxon's two-sample test.
† $P = 0.05$ by Wilcoxon's two-sample test.
‡ Gram-negative bacteria involved were *Enterobacter cloacae* for SAM patients and *Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella pneumoniae* for patients receiving placebo.

Table 5. Antimicrobial therapy in patients with acute nonlymphocytic leukemia who received a regimen of selective antimicrobial modulation (SAM) or placebo.

	SAM group (16)		Placebo group (17)	
Antimicrobial agent	No. of patients	Days of therapy*	No. of patients	Days of therapy*
Aminoglycoside†	6	7 (2–41)	8	14 (2–19)
Cephalosporin‡	3	3 (1–4)	8	8.5 (3–24)
Penicillin§	10	9.5 (3–34)	8	7.5 (3–14)
Trimethoprim-sulfamethoxazole	4	11 (9–14)	3	14 (4–14)
Miscellaneous	5	11 (5–17)	9	11.5 (6–53)
No drug	3	. . .	2	. . .
One drug	6	. . .	1	. . .
Two or more drugs	7	. . .	14	. . .

* Median no. of days (range) on which the indicated therapy was administered.

† Tobramycin in 12 patients and gentamicin in two patients.

‡ Cefamandole.

§ Penicillin G in 13 patients, cloxacillin in four patients, and ampicillin in one patient.

Although no differences were shown in the first week of prophylactic treatment, a decrease ($P = 0.05$) in the number of acquired major infections was observed in the SAM patients during the remaining period compared to the patients receiving placebo (table 4). Two of the three major infections acquired by the SAM patients were caused by microorganisms that are intrinsically insensitive to the SAM regimen—septicemia due to *Streptococcus pneumoniae* and a rectal infiltrate probably caused by anaerobic bacteria and *Streptococcus faecalis*. In the third patient, septicemia with *E. cloacae* occurred. This infection was considered to be of exogenous origin—a secondarily infected herpes labialis lesion. Among the controls there were seven cases of septicemia due to gram-negative organisms, most of which probably originated from the oropharyngeal or rectal regions; one of these patients also developed pneumonia caused by *Legionella pneumophila*.

No differences were found between the SAM group and the placebo group with respect to local and doubtful infection. Evidence of viral infection was obtained in two SAM patients; those infections were due to herpes simplex virus, one of which was associated with a secondary bacterial infection as mentioned above. In the patients given placebo, lesions due to herpes simplex virus became secondarily infected with *Klebsiella pneumoniae*.

Antibiotic use. The reduction of infectious complications in the SAM group was associated with a reduction of the use of both aminoglycosides and cephalosporins; the use of penicillin, trimethoprim-sulfamethoxazole, and other antibiotics was not lower than that in the placebo group (table 5). Aminoglycosides were administered for the treatment of an assumed infection in six SAM patients, and retrospective analysis reveals that this had not been necessary in at least four of them.

Fever. Although the reduction of the incidence of major infection in the SAM group in comparison to the placebo group is obvious, the effect on fever is less pronounced. In the SAM group, fever occurred on a mean of 9.5 days (19%) during the mean prophylaxis period of ~50 days, whereas fever occurred on 14 days (31%) during the mean prophylaxis period of 45 days for the patients given the placebo. To find out whether this difference was associated with a reduced incidence of infection, only days with fever during the risk period (granulocyte counts, $<500/mm^3$) were considered for statistical evaluation. Single days during which a patient's fever was probably not associated with infection (total, nine days for the SAM group and 26 days for the placebo group) and days with fever occurring after the termination of prophylaxis or placebo were not included.

In the SAM group, 22 granulocytopenic episodes occurred, of which eight were not associated with fever; in the control group, 20 granulocytopenic episodes occurred, of which seven were not associated with fever. The mean duration of the granulocytopenic episodes without fever was about 18 days for both groups. The duration of the other granulocytopenic episodes—those that were associated with fever—was longer, amounting to a mean of 28 and 26 days for the SAM and placebo groups, respectively (figure 1). In the SAM group, fever occurred during about 11 (41%) of these days, as compared with 13.5 (52%) days for the control group. If only days with high fever (axillary temperature, >39 C) are taken into account, the difference in the mean number of days with fever (four and 6.5 days for the SAM and control groups, respectively) is significant ($P = 0.05$).

Bacteriologic evaluation. The results obtained from the cultures of fecal samples obtained once

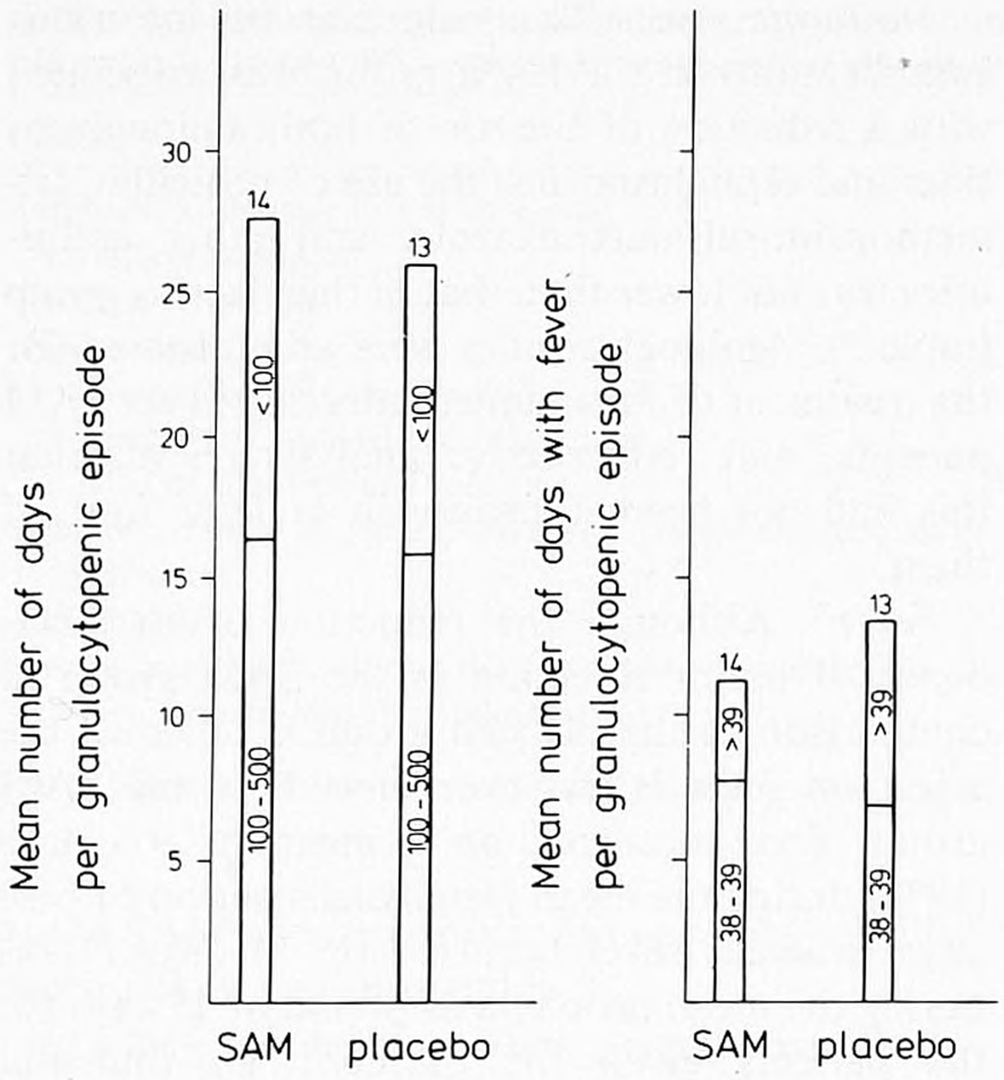

Figure 1. Mean duration of granulocytopenic episodes associated with fever in patients with acute nonlymphocytic leukemia who received a regimen of selective antimicrobial modulation (SAM) or placebo. The bars representing the no. of days per granulocytopenic episode (*left*) are divided into days with granulocyte counts of 100–500/mm³ and days with counts of <100/mm³. The bars representing the no. of granulocytopenic days with fever per granulocytopenic episode (*right*) are divided into days with an axillary body temperature of 38–39 C and days with a temperature of >39 C. The nos. of granulocytopenic episodes evaluated in each group are indicated above the bars.

a week are shown in figure 2. On the first day of prophylaxis, aerobic gram-negative rods were cultured from almost all fecal samples. After the first week the aerobic gram-negative rods had been eliminated from the stools of most SAM patients, and the fecal cultures only incidentally were found to contain aerobic gram-negative bacteria; in contrast, almost all fecal samples from the placebo group contained gram-negative bacteria. The gram-negative bacteria shown in the fecal samples of SAM patients were sensitive to the antimicrobial drugs in the SAM regimen; they were transient, or, if they persisted temporarily, the failure was associated with an interruption of the intake of the SAM regimen. Although the antibacterial activity of the SAM regimen was solely localized in the intestines, a reduction of aerobic gram-negative rods also occurred in the oral cavity and the genitourinary region and on the skin. *E. coli* was cultured from swabs taken from these locations (figure 3) in ~25% of the swabs in the SAM group and in 95% of the swabs in the placebo group. For *Klebsiella* species, the percentages of positive swabs were 10% in the SAM group and 20% in the placebo group, and for other Enterobacteriaceae, 5% and 40%, respectively. *Pseudomonas aeruginosa* was cultured from ~1% of the swabs in the SAM group and in 15% of the swabs in the placebo group. As in the cultures of the fecal samples, these gram-negative rods were often transient in the SAM group in contrast to the placebo group.

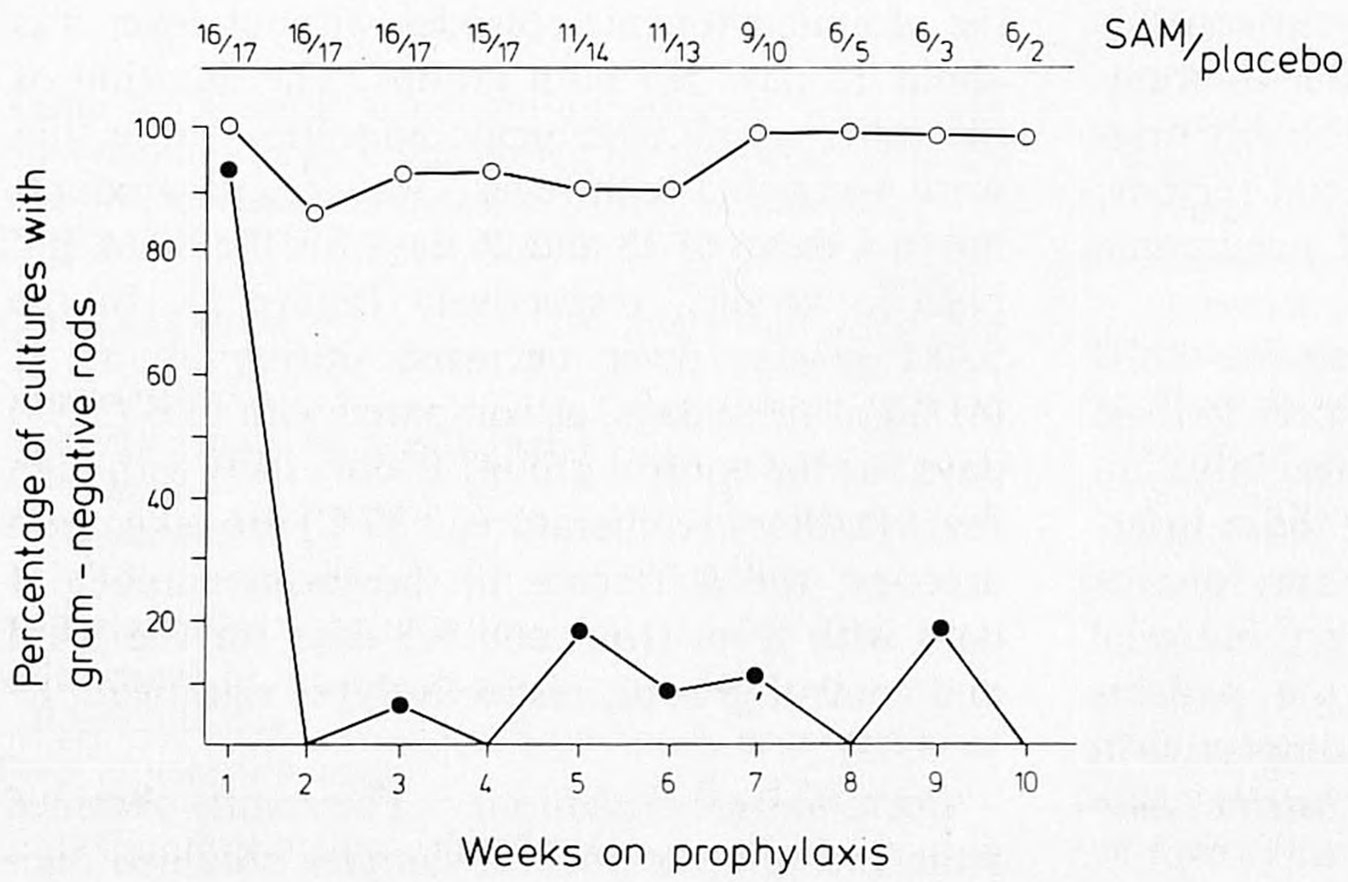

Figure 2. Percentage of cultures with aerobic and facultative anaerobic gram-negative rods cultured from stool samples of patients with acute nonlymphocytic leukemia who received a regimen of (●) selective antimicrobial modulation (SAM) or (○) placebo. The nos. of samples cultured are indicated at the top of the figure.

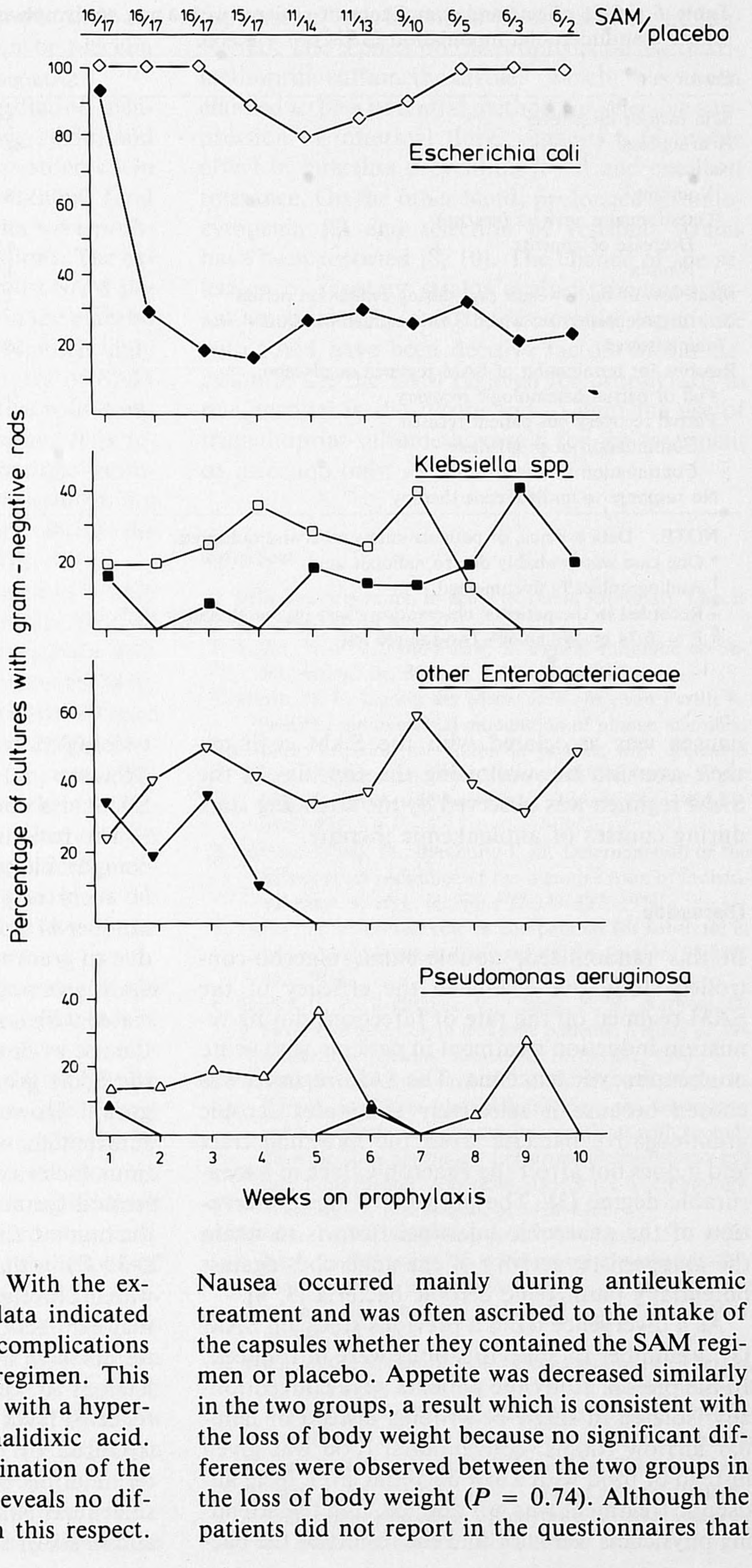

Figure 3. Percentages of aerobic and facultative anaerobic gram-negative rods cultured from swabs of the oral cavity, genitourinary region, and skin of patients with acute nonlymphocytic leukemia who received a regimen of (solid figures) selective antimicrobial modulation (SAM) or (open symbols) placebo. The nos. of samples cultured are indicated at the top of the figure.

Complications and compliance. With the exception of one case, none of the data indicated that either more or fewer important complications had to be attributed to the SAM regimen. This single exception concerned a patient with a hypersensitivity reaction, probably to nalidixic acid. Comparison of the reasons for termination of the SAM regimen or placebo (table 6) reveals no differences between the two groups in this respect. Nausea occurred mainly during antileukemic treatment and was often ascribed to the intake of the capsules whether they contained the SAM regimen or placebo. Appetite was decreased similarly in the two groups, a result which is consistent with the loss of body weight because no significant differences were observed between the two groups in the loss of body weight ($P = 0.74$). Although the patients did not report in the questionnaires that

Table 6. Side effects and compliance of patients with acute nonlymphocytic leukemia who received a regimen of selective antimicrobial modulation (SAM) or placebo.

Factor	SAM group (16)	Placebo group (17)
Skin rash or drug fever	5*	9
Hearing loss†	2	2
Nausea		
Vomiting‡	8	8
Questionnaire answers (yes/no)		
Decrease of appetite	4/5	7/5
Nausea	4/5	3/9
Mean loss of body weight (kg) during evaluation period	2.35§	1.48§
No. of patient-days on which SAM regimen or placebo was administered	50.4	45.5
Reasons for termination of SAM regimen or placebo		
Full or partial hematologic recovery	9	8
Partial recovery but patient refused		
Continuation of prophylaxis	2	1
Continuation of barrier nursing	2	3
No response to antileukemic therapy	3	5

NOTE. Data are nos. of patients unless otherwise indicated.
* One case was probably due to nalidixic acid.
† Audiographically documented.
‡ Recorded in the patients' observation chart by the attending staff.
§ $P = 0.74$ by Wilcoxon's two-sample test.

nausea was associated with the SAM regimen, their aversion to swallowing the capsules in the SAM regimen was observed by the attending staff during courses of antileukemic therapy.

Discussion

In this randomized, double-blind, placebo-controlled study, we evaluated the efficacy of the SAM regimen on the rate of infections during remission-induction treatment in patients with acute nonlymphocytic leukemia. The SAM regimen was chosen because it selectively eliminates aerobic gram-negative bacteria from the intestinal tract and it does not affect the anaerobic flora to a measurable degree [3]. The purpose of the preservation of the anaerobic intestinal flora is to retain the antagonistic activity of the anaerobes against potentially pathogenic aerobic bacteria [3, 4].

As a divergence from a previous study on SAM [3], a number of simplifications were introduced. In the present study the patients were conventionally isolated in single-bed rooms instead of laminar airflow rooms, conventional food was given instead of food with a low bacterial level, local antiseptic treatment was not applied, and the attending physicians were not told the results of the bacteriologic surveillance cultures. These simplifications were introduced to evaluate the feasibility of SAM in a conventional hospital environment.

The patients assigned to the SAM group were comparable to the patients who received placebo in every respect. A significant reduction in the number of patients with acquired major infections due to gram-negative organisms was shown in the SAM group. This reduction of infection was associated with a reduction of fever and a reduction in the use of aminoglycosides and cephalosporins in the SAM group in comparison with the placebo group. However, this reduction of fever is not substantial, which suggests that many noninfectious factors are involved in the fever of patients treated for acute myelogenous leukemia. The reduction of the number of days with high fever (>39 C) in the SAM group is significant, a result which correlates with the observed reduction of major infectious complications. Almost the same results were obtained in a previous study [7]. Objections to the method of evaluation of the occurrence of fever, based on the possibility of bias introduced by exclusion of fever continuing after termination of SAM or placebo, are refutable, since fever continued in one of three SAM patients and in six of seven patients who received placebo,

all of whom continued to be granulocytopenic after termination of the SAM regimen or placebo capsules.

As a consequence of the limited isolation measures, contamination of the oral cavity, skin, and genitourinary region was frequently observed in the present study. The use of conventional food and the omission of topical antiseptics were probably responsible for these contaminations. The exogenous bacteria were transient in most SAM patients, whereas they persisted longer in the placebo group. Because of the prophylactic regimen, only a small proportion of the fecal cultures of SAM patients showed aerobic gram-negative rods compared with those of the placebo group. It is remarkable that the elimination of aerobic gram-negative rods from the intestines also resulted in a reduction of these bacteria in the oral cavity, the genitourinary region, and on the skin.

The lack of adequate isolation measures is only reflected by infection with herpes simplex virus in one SAM patient. In this patient, septicemia with *E. cloacae* could probably have been prevented by better isolation. Routine bacteriologic surveillance cultures in SAM patients would probably contribute to the choice of adequate antimicrobial therapy in case of infection and to the maintenance of the quality of prophylaxis. However, in the present study antimicrobial drugs were probably given more often than really needed in the SAM group because of the inaccessibility of the results of surveillance cultures.

In general, tolerance to the ingestion of the SAM regimen was reasonable. Of course, most of the patients did not like having to swallow the capsules and tablets four times a day, but objective observations (patients' observation cards and questionnaires) did not show substantial differences between tolerance in the two groups. No signs of toxicity, diarrhea, or other complications attributable to the SAM regimen were observed.

It can be concluded that in general the results of the present study confirm the findings of the previous study on SAM [3], indicating that major infections with gram-negative microorganisms can be prevented by SAM. The prophylactic regimen mainly reduces morbidity; a favorable effect on remission rate and survival was not found for the small number of patients in this study.

The question of whether the SAM regimen is superior or inferior to other regimens for selective suppression of intestinal flora cannot be answered. The reports on the prophylactic use of trimethoprim-sulfamethoxazole, which has been claimed to be a potential method for selective suppression of intestinal flora, suggests a favorable effect in infection prevention [8, 9] and excellent tolerance. On the other hand, prolonged granulocytopenia [8] and selection of resistant strains have been reported [8, 10]. The chance of the selection of resistant strains against trimethoprim-sulfamethoxazole and the favorable experience with SAM have been decisive factors in our decision to use the SAM regimen for prophylaxis in our hospital in the future and to limit the use of trimethoprim-sulfamethoxazole for the treatment of infection only.

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